--44. (amended) A method of diagnosing or evaluating human cancer in a patient comprising:

measuring the level of amplification or expression of a MAC117 gene in a sample from said patient[; and

classifying those patients having an increased level of amplification or expression of said gene as being likely to suffer from cancer] , the presence of amplification or increased expression of said MAC117 gene indicating the presence of cancer.

REMARKS

Claims 14, 26, 29, 40, 41 and 44-60 were pending in the application. Claims 14, 26, 29, 40, 41, 48-59 have been canceled hereinabove. Therefore, claims 44-47 and 60 are currently pending. Applicants note a request for interference and a phantom count was proposed in a previous Office Action. The Examiner stated that the Examiner will make an interference determination after allowable subject matter is found.

Claim 44 has been amended to delete new matter objected to by the Examiner in the final Office Action. In addition, claim 44 has been amended to add the proper method claim phrase that the presence of amplification or increased expression indicates the presence of cancer. This phrase merely clarifies the claim by adding a conclusory phrase and therefore cannot add new matter or require further consideration.

In view of the above amendments and following remarks, reconsideration and withdrawal of the remaining rejections is respectfully requested.

Applicants acknowledge the Examiner's clarification of the terms "diagnosis" and "prognosis." However, applicants point out that a prognosis necessarily requires one or more diagnostic events.

In the Office Action, various phrases were objected to as allegedly presenting new matter. To advance the prosecution of the application, the phrases have been deleted from claim 44. The remaining claims containing the objectionable phrasing have been canceled. Applicants reserve the right to prosecute the canceled claims in another application. In view of these amendments, withdrawal of this objection is respectfully requested.

In the sole remaining rejection, claims 14, 40 and 60 stand rejected under 35 U.S.C. § 101 as allegedly lacking utility due to lack of evidence supporting the cancer diagnostic utility as claimed.

Applicants respectfully traverse this rejection. Applicants initially wish to clarify the nomenclature used to identify the gene of interest. The subject specification and

claims refer to the gene as the MAC117 gene. However, the gene is now referred to in the literature as *erb*B-2. The gene has also been called HER-2 and Neu in the past.

A review of the literature clearly demonstrates that erbB-2 can be used to diagnose cancer. *erb*B-2 has been defined as a proto-oncogene in the most widely accepted and stringent test system, namely NIH3T3 cell transfection. By definition, proto-oncogenes become activated as oncogenes only in malignancies, but not in normal cells (Varmus H.E. Ann. Rev. Genet. 18:553, 1984) (a copy of which is attached hereto). Thus, since *erb*B-2 can be an oncogene, it must be <u>diagnostic</u> for a tumor when expressed as an oncogene.

Mechanistically, *erb*B-2 has been identified as a proto-oncogene *in vivo* and *in vitro* (Bargmann et al. Cell 45:649, 1986; De Fiore et al. Science 237:178, 1987; Hudziak et al. PNAS 84:7159, 1987; Muller et al. Cell 54:105, 1988) (copies of these references are attached hereto). Mechanisms activating cellular proto-oncogenes to oncogenes include gene amplification, gene rearrangement and point mutations. While these mechanisms are capable of activating *erb*B-2 as an oncogene *in vitro* and in an animal model system, the predominant alteration observed in human tumors is gene amplification accompanied by overexpression of the mRNA and protein. Applicants and others have directly demonstrated that the same alterations that occur in human tumors

activate *erb*B-2 as an oncogene (Di Fiore et al., *id.*; Hudziak et al., *id.*). These observations teach that the oncogenicity of the structurally normal *erb*B-2 coding sequence is strictly dependent on the expression level. More directly, the references demonstrate that *erb*B-2 expression levels observed in human malignancies in which the gene is amplified are sufficient for its oncogenicity. Furthermore, oncogenic *erb*B-2 has been shown to causally induce mammary cancer *in vivo* (Muller et al., *id.*).

Direct demonstration for *erb*B-2 alterations to be tumor specific also derives from *in situ* methodologies including immunohistochemistry and cytohybridization. In such studies *erb*B-2 overexpression occurs only in tumor cells but not non-malignant interstitial cells or nonmalignant epithelium. Examples are found in Paik et al. J. Clin. Oncol. 8:103, 1990 and Inglehart et al. Cancer Research 50:6701, 1990 (copies of which are attached hereto). Careful titration of *erb*B-2 protein levels in normal breast epithelium and breast cancer tissue (Lacroix et al. Oncogene 4:145, 1989 (a copy of which is attached hereto); Inglehart et al., *id.*) demonstrates that normal breast epithelium expresses low levels of *erb*B-2 protein from which tumor cells harboring moderate or high levels of overexpression can be clearly discerned. The latter tumors consistently harbored gene amplification.

Finally, several studies exist which demonstrate large numbers of normal or nonmalignant controls which did not show *erb*B-2 amplification or associated overexpression. Yokota et al. Lancet 1:765, 1986 (attached hereto) investigate 70 normal donors for gene amplification, Zhou et al. Cancer Res. 47:6123-6125, 1987 (attached hereto) disclose 11 normal donors, Varley et al. Oncogene 1:432, 1987 (attached hereto) investigate 10 cases with benign fibrocystic disease. A more recent study (Press et al. Oncogene 5:953, 1990) (attached hereto) has comprehensively analyzed a large collection of normal adult tissues including 21 normal breast specimens for *erb*B-2 aberrations at the genomic, transcript and protein level. This analysis was conducted in comparison to typical cases of tumor-associated *erb*B-2 gene amplification and overexpression. No alterations were observed in any normal tissue, thus adding to abundant mechanistic and phenomenological evidence that abnormalities affecting *erb*B-2 are tumor specific.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

No additional fee is believed due. However, the Commissioner is hereby authorized to charge any additional fees

which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

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David G. Perryman

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